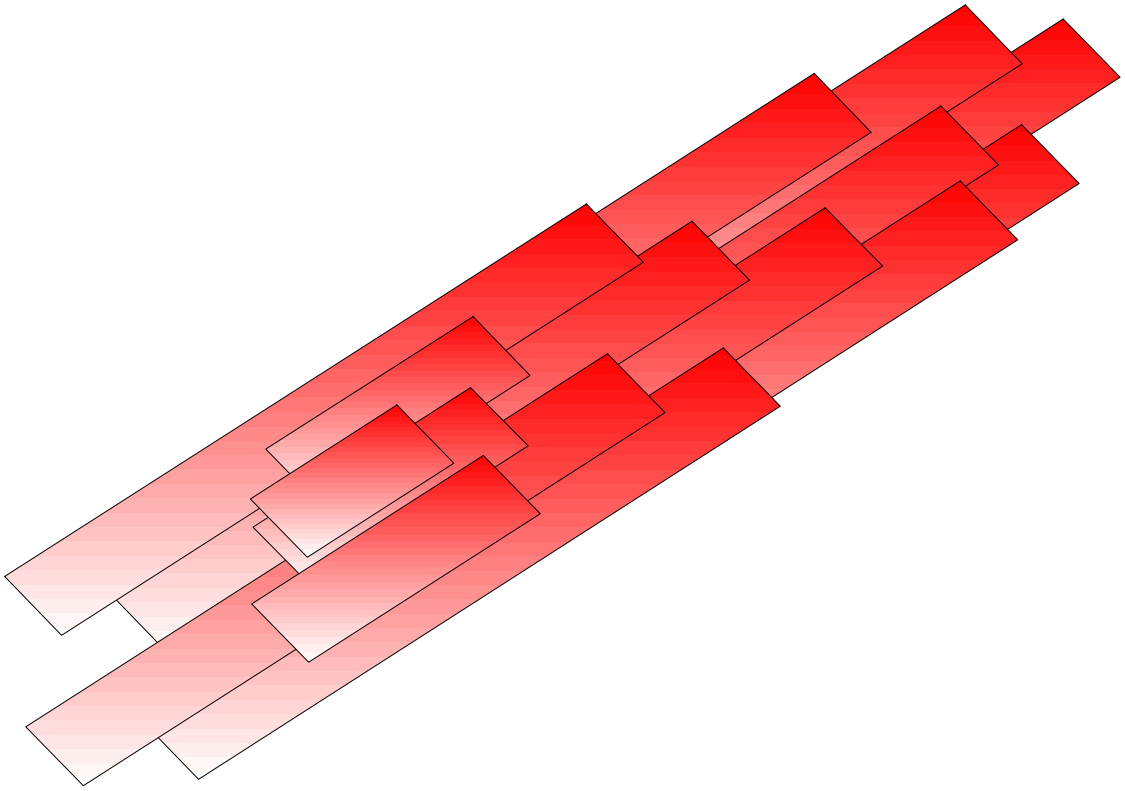
Guideline for Industry

Impurities in New Drug Substances



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GUIDELINE FOR INDUSTRY[1]

IMPURITIES IN NEW DRUG SUBSTANCES

I. PREAMBLE (1)

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to the regulation of new drug substances used during the clinical research stage of development. Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered. Impurities in new drug substances are addressed from two perspectives:

- Chemistry aspects include classification and identification of impurities, report generation, setting specifications, and a brief discussion of analytical procedures; and

- Safety aspects include specific guidance for qualifying impurities which were not present in batches of new drug substance used in safety and clinical studies and/or impurity levels substantially higher than in those batches. Threshold limits are defined, below which, qualification is not needed.

II. CLASSIFICATION OF IMPURITIES (2)

Impurities may be classified into the following categories:

- Organic Impurities (Process and Drug Related)
- Inorganic Impurities
- Residual Solvents

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[1]This guideline was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, March 1995. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA. This guideline was published in the *Federal Register* on January 4, 1996 (61 FR 371) and is applicable to drug and biological products. Although this guideline does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a country, region, or member state. For additional copies of this guideline, contact the Drug Information Branch, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573) or the Manufacturers Assistance and Communication Staff (HFM-42), CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the offices in processing your request. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW) (connect to the CDER Home Page at http://www.fda.gov/cder and to the "Regulatory Guidance" section).

Organic impurities may arise during the manufacturing process and/or storage of the new drug substance. They may be identified or unidentified, volatile or nonvolatile, and include:

- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands, and Catalysts

Inorganic impurities may derive from the manufacturing process. They are normally known and identified, and include:

- Reagents, Ligands, and Catalysts
- Heavy Metals
- Inorganic Salts
- Other Materials (e.g., Filter Aids, Charcoal, etc.)

Solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

Excluded from this document are: Extraneous contaminants which should not occur in new drug substances and are more appropriately addressed as good manufacturing practice issues; polymorphic form, a solid state property of the new drug substance; and enantiomeric impurities.

III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES (3)

A. Organic Impurities (3.1)

The applicant should summarize those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials which could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion may only include those impurities that may reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as results of intentional degradation studies used to identify potential impurities that arise during storage. Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing. The impurity profile of the

drug substance lots intended for marketing should be compared with those used in development and any differences discussed.

The studies conducted to characterize the structure of actual impurities present in the new drug substance at or above an apparent level of 0.1 percent (e.g., calculated using the response factor of the drug substance) should be described. Note that all recurring impurities at or above the 0.1 percent level in batches manufactured by the proposed commercial process should be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities below the 0.1 percent level, it is useful to also report the results of these studies.

Identification of impurities below apparent levels of 0.1 percent is generally not considered necessary. However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level lower than 0.1 percent. In all cases, impurities should be qualified as described later in this guide. Although it is common practice to round analytical results of between 0.05 and 0.09 percent to the nearest number (i.e., 0.1 percent), for the purpose of these guidelines, such values would not be rounded to 0.1 percent and these impurities would not require identification.

B. Inorganic Impurities (3.2)

Inorganic impurities normally are detected and quantitated using pharmacopeial or other appropriate procedures. Carry over of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specifications should be discussed. Limits should be based on pharmacopeial standards or known safety data.

C. Solvents (3.3)

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed. Any solvents which may appear in the drug substance should be quantified using analytical procedures with an appropriate level of sensitivity. Pharmacopeial or other appropriate procedures should be utilized. Limits should be based on pharmacopeial standards or known safety data taking into consideration dose, duration of treatment, and route of administration. Particular attention should be given to quantitation of toxic solvents used in the manufacturing process.

IV. ANALYTICAL PROCEDURES (4)

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of impurities. Differences in the analytical procedures used during development and proposed for the commercial product should be discussed in the registration application.

Organic impurity levels can be measured by a variety of techniques, including those which compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. The drug substance may be used to estimate the levels of impurities. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Specifications and analytical procedures used to estimate identified or unidentified impurities often are based on analytical assumptions (e.g., equivalent detector response, etc.). The assumptions should be discussed in the registration application.

V. REPORTING IMPURITY CONTENT OF BATCHES (5)

Analytical results should be provided for all batches of the new drug substance used for clinical, safety, and stability testing, as well as batches representative of the proposed commercial process. The content of individual identified and unidentified and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time. Levels of impurities which are present but are below the validated limit of quantitation need not be reported. When analytical procedures change during development, reported results should be linked with the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of such representative batches, from methods validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (i.e., chromatograms) of individual batches are available if requested. A tabulation should be provided which links the specific new drug substance batch to each safety study and each clinical study in which it has been used.

For each batch of the new drug substance, the report should include:

- Batch Identity and Size
- Date of Manufacture
- Site of Manufacture
- Manufacturing Process
- Impurity Content, Individual and Total
- Use of Batches
- Reference to Analytical Procedure Used

VI. SPECIFICATION LIMITS FOR IMPURITIES (6)

The specifications for a new drug substance should include limits for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities to include in the new drug substance specifications should be based on the impurities found in batches manufactured by the proposed commercial process. Those impurities selected for inclusion in the specifications for the new drug substance are referred to as "specified impurities" in this guideline. Specified impurities may be identified or unidentified and should be individually listed in the new drug substance specifications.

A rationale for the inclusion or exclusion of impurities in the specifications should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of material manufactured by the proposed commercial process. Specific identified impurities should be included along with recurring unidentified impurities estimated to be at or above 0.1 percent. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical methods should be commensurate with the level at which the impurities must be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Unidentified impurities included in the specifications should be referred to by some appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). Finally, a general specification limit of not more than 0.1 percent for any unspecified impurity should be included.

Limits should be set no higher than the level that can be justified by safety data, and, unless safety data indicate otherwise, no lower than the level achievable by the manufacturing process and the analytical capability. In other words, where there is no safety concern, impurity specifications should be based on data generated on actual batches of the new drug substance allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels may indicate that the manufacturing process of the new drug substance is not adequately controlled and validated. In summary, the new drug substance specifications should include, where applicable, limits for:

Organic Impurities:

- Each Specified Identified Impurity
- Each Specified Unidentified Impurity at or above 0.1 percent
- Any Unspecified Impurity, with a limit of not more than 0.1 percent
- Total Impurities

Residual Solvents

Inorganic Impurities

A summation of assay value and impurity levels generally may be used to obtain mass balance for the test sample. The mass balance need not add to exactly 100 percent because of the analytical error associated with each analytical procedure. The summation of impurity levels plus the assay value may be misleading, for example, when the assay procedure is nonspecific (e.g., potentiometric titrimetry) and the impurity level is relatively high.

VII. QUALIFICATION OF IMPURITIES (7)

Qualification is the process of acquiring and evaluating data which establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for selecting impurity limits based on safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies is considered qualified. Impurities that are also significant metabolites present in animal and/or human studies do not need further qualification. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous safety studies.

If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed when the usual qualification threshold limits given below are exceeded:

Maximum daily dose	Qualification threshold
<1s-thn-eq> 2 grams (g)/day.....	0.1 percent or 1 milligram per day intake (whichever is lower)
> 2 g/day.....	0.05 percent

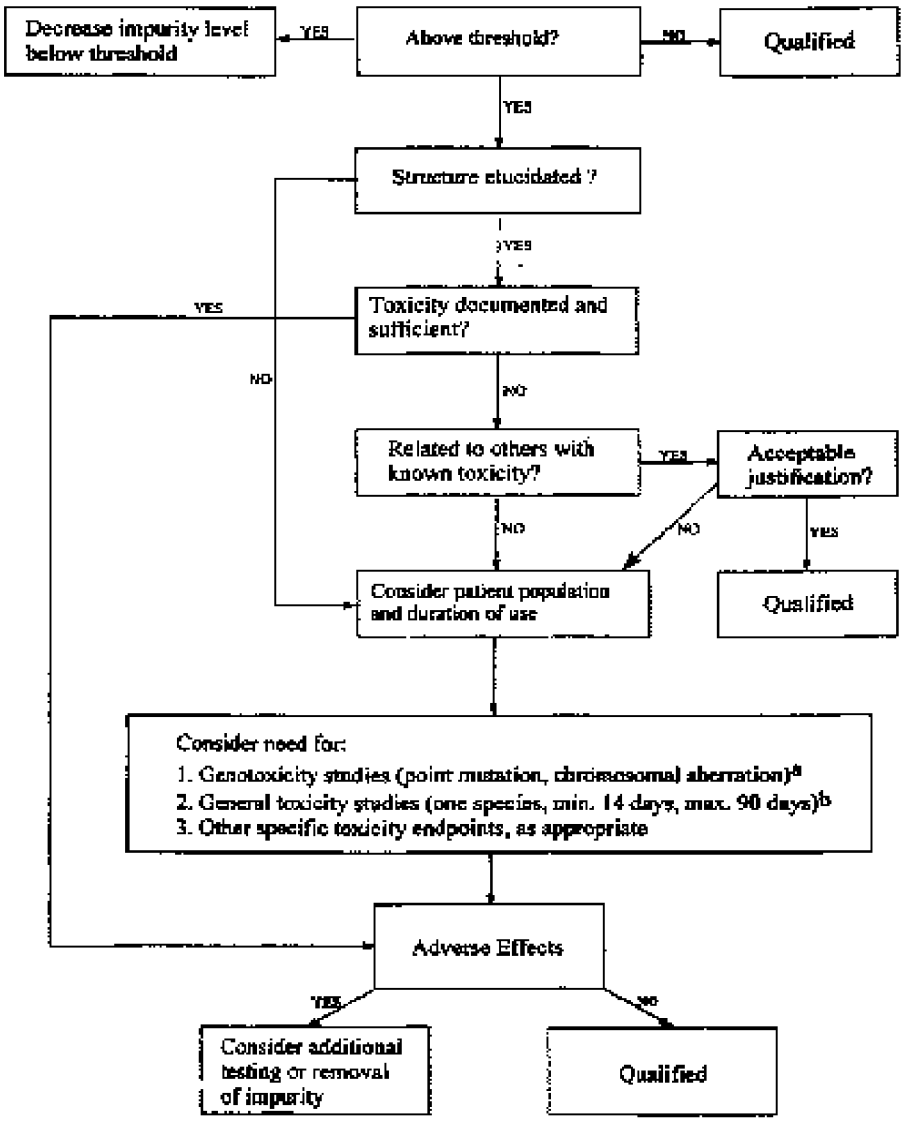
Higher or lower threshold limits for qualification of impurities may be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification may be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold limit may be appropriate. Conversely, a higher qualification threshold limit may be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations). Technical factors (manufacturing capability and control methodology) may be considered as part of the justification for selection of alternative threshold limits. Proposals for alternative threshold limits are considered on a case-by-case basis.

The “Decision Tree for Safety Studies” (Figure 1) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity below the threshold may be simpler than providing safety data. Alternatively, adequate data may be

available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies desired to qualify an impurity will depend on a number of factors, including the patient population, daily dose, route, and duration of drug administration. Such studies are normally conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities are seen as acceptable.

Figure 1

DECISION TREE FOR SAFETY STUDIES



[a]If considered desirable, a minimum screen for genotoxic potential should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are seen as an acceptable minimum screen.

[b]If general toxicity studies are desirable, study(ies) should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days are seen as acceptable.

VIII. NEW IMPURITIES (8)

During the course of a drug development program, the qualitative impurity profile of the new drug substance may change, or a new impurity may appear as a result of, for example, synthetic route changes, process optimization, or scale-up. New impurities may be identified or unidentified. Such changes call for consideration of the need for qualification of the level of the impurity, unless it is below the threshold values as noted above. When a new impurity exceeds the threshold, the "Decision Tree for Safety Studies" should be consulted. Safety studies should compare the new drug substance containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also seen as acceptable (these studies may not always have clinical relevance).

ATTACHMENT A

GLOSSARY (9)

Chemical Development Studies: Studies conducted to scale-up, optimize, and validate the manufacturing process for a new drug substance.

Enantiomers: Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Extraneous Substance: An impurity arising from any source extraneous to the manufacturing process.

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin may also be present.

Identified Impurity: An impurity for which a structural characterization has been achieved.

Impurity: Any component of the new drug substance which is not the chemical entity defined as the new drug substance.

Impurity Profile: A description of the identified and unidentified impurities present in a new drug substance.

Intermediate: A material produced during steps of the synthesis of a new drug substance which must undergo further molecular change before it becomes a new drug substance.

Ligand: An agent with a strong affinity to a metal ion.

New Drug Substance: The designated therapeutic moiety which has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism: The occurrence of different crystalline forms of the same drug substance.

Potential Impurity: An impurity which, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the new drug substance.

Qualification: The process of acquiring and evaluating data which establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Reagent: A substance, other than a starting material or solvent, which is used in the manufacture of a new drug substance.

Safety Information: The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified Impurity: Identified or unidentified impurity that is selected for inclusion in the new drug substance specifications and is individually listed and limited in order to assure the safety and quality of the new drug substance.

Starting Material: A material used in the synthesis of a new drug substance which is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials normally are commercially available and of defined chemical and physical properties and structure.

Toxic Impurity: Impurities having significant undesirable biological activity.

Unidentified Impurity: An impurity which is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Validated Limit of Quantitation: For impurities at a level of 0.1 percent, the validated limit of quantitation should be less than or equal to 0.05 percent. Impurities limited at higher levels may have higher limits of quantitation.